between the two groups?

DR. CUTLER: We haven't looked at that.

DR. LINDENFELD: It just seems to me here we have this problem between no difference in mortality and all these heart failure deaths, and doxazosin has been said to improve insulin sensitivity. So if we saw a difference in the incidence of new diabetes, that might completely change how we viewed -- and I think that's -- Given what you thought about this drug at the beginning, I think that's a very important piece of information to have.

ACTING CHAIRMAN BORER: Bob?

DR. TEMPLE: Do you know the answer to Bob Fenichel's question? Was there a lesser degree of control to the desired endpoint as well as a difference in average, or not?

DR. CUTLER: I think there was a few percentage points difference. You have that -- Overall, the systolic blood pressure control across the arms was in the range of 60 percent.

DR. FLEMING: I think at one year it was 61 against 54. At four years, it was 64 against 58.

DR. TEMPLE: It's easier to translate the millimeters of mercury to a difference in risk than

that, but it sounds like they are showing about the same thing.

ACTING CHAIRMAN BORER: I have one question here, and it's really more for our two statisticians and perhaps the NIH statisticians.

A lot was made in our materials about a doubling of risk and, in fact, Tom, you used that terminology in asking one of your questions, that CHF risk or frequence was doubled.

Just for my own edification, I want to understand how confident we can be in the concept, in the belief that the rate of congestive heart failure development was doubled.

My understanding is that -- and you must correct me if I'm wrong -- that in a clinical trial, the finding of sufficient consistency between outcomes allows you to say that it's unlikely that that difference is due to chance alone. The determination of the believability of the absolute point estimate, as I understand it, is determined by other criteria, by precision, by the size of the standard error, the size of the standard deviation.

So given that, and given the fact that there are confidence limits that we saw -- they don't overlap, but they are there -- and given the fact that

there are multiple potential confounding factors, additional drugs, change in drugs, not taking drugs, this, that and the other thing, difference in blood pressure control, stopping the trial, this arm of the trial, in the middle rather than going out to the end, how confident can we be in the magnitude of the difference between the doxazosin arm and the chlorthalidone arm in terms of frequency of heart failure?

You may want to respond to that first, Dr. Cutler, and then maybe we have some committee members.

DR. CUTLER: Well, the confidence limits are right there at the end of that graph and in the paper. They are low 1.79, high 2.32. So pretty tight confidence limits, really.

ACTING CHAIRMAN BORER: Tom, can you respond?

DR. FLEMING: Well, I think maybe we'll get into some of the issues that you have raised, Jeff, in more depth this afternoon as you try to put all of these results into the context of primary and secondary analyses and interim analyses and the influence of that, the influence of additional interventions being delivered.

I guess I would say, in general, the study

is designed to address a strategy of delivery of an alpha blocker against diuretics with additional supportive care as needed. One of the great strengths of the study is it's a very large size and, as Dr. Cutler had pointed out, high precision in the estimate.

I don't know if Ralph has any additional comments, but some of these issues we'll certainly get back to more this afternoon.

DR. D'AGOSTINO: I think the issues will get back, especially the way the sequence of questions are laid out. But I do think, you know, at this particular point, not so much as a summary because you gave quite a nice summary in terms of what the issues are, but to give another perspective from the statistics point of view: When you are looking at -- When I'm looking at trials such as this, it's a complicated trial -- there are a number of treatments; number of possible comparisons -- you look very to ask the question what were the rules for stopping? What were the predetermined decision rules?

If I read the materials correctly, and I stand to be corrected -- If I read the materials correctly, there was talk about this notion of superiority and stopping for the futility. I do have

a problem of why would this be -- why is this a superiority as opposed to noninferiority. But they did sort of address that.

What I don't find in any of the materials is how they are going to grapple with interim looks at efficacy variables and interim look at safety data. I'm not sure what they thinking of in terms of the CHF. Are they thinking of it as a safety problem or are they thinking of it as efficacy? It's both in this case here.

You know, when I've served on these data safety monitoring committees, as a number of us have done, quite often with the safety you sort of just keep looking at the adverse events and, if you see something that looks really bizarre and problematic, you sort of chase it down.

I get the flavor -- and I would, again, like to hear more about it. I get the flavor that it was more driven by that type of a sequence, that they looked at the overall, but there was the safety that was beginning to emerge. It gets very hard to interpret these results.

I mean, I think it's almost -- In terms of the statistical p-values that you attach to it, it's almost to a point where -- and I hope we do have more

discussion -- that maybe there's something meaningless exercise in terms of saying does the p-value have interpretation as opposed to is the safety issue so serious that, no matter how we look at the data, it's going to maintain itself.

I think questions like the diagnoses are very important, questions like what happens if you follow those who really took the drug, what happens if you collected more data. Then what happens around the whole study? I mean, how many other events, how many other endpoints were problematic? What did the committee have? What did this independent committee have that we don't have?

I think, to try to interpret these numbers, you really need that context. It's not -- I don't think you can focus on this confidence interval and say that's a 95 percent confidence interval; therefore, it's there. There's lots of uncertainty that you have to start attributing to it.

If it really is safety as opposed to efficacy, then I think we're in a real bind in terms of interpreting it. if it's an efficacy, then you have to ask the question, well, you saw nothing in the primary; how do you start interpreting secondary variables?

I'm not giving you a definite answer in terms of how do you interpret it, outside of saying that it's not easy to interpret, and I think we have a lot of discussion on dealing with this.

ACTING CHAIRMAN BORER: Ray?

DR. LIPICKY: Can you suggest what should be looked at to try to differentiate between whether there was irreversible harm? Let me put it in this sense. Let's say that both the people in the chlorthalidone arm and the people in the doxazosin arm were developing the same degree of myocardial function abnormality, and that chlorthalidone, which is a treatment for heart failure, didn't allow the symptoms to develop, so it didn't get diagnosed; that doxazosin, which isn't a treatment for heart failure, let the symptoms be diagnosed. So that we ought to regard this difference as reports of heart failure, not as heart failure in the sense of having caused an irreversible change in myocardial function.

What data should we look at to tell whether that's true or whether, in fact, people in doxazosin arm lost more cells or had a bigger decrease in contractility or had some remodeling problem or something like that, and that irreversible harm was actually caused?

DR. CUTLER: There won't be a lot more -- You know, there won't be a lot of mechanism data coming from ALLHAT, because of the nature of the trial. We can show you more detail on the ejection fraction, for example, if you care. But beyond that, there is not a whole lot.

DR. LIPICKY: But only in the people who had heart failure diagnosed.

DR. CUTLER: That's right. These were not routinely done as part of follow-up.

DR. LIPICKY: So in fact, the data won't allow the differentiation between those two possibilities, and one can't take the inference that irreversible harm was a part of the reporting of increase in congestive heart failure.

DR. CUTLER: Well, the one thing that we can do and may do is do continued mortality follow-up on these cohorts, and that may be --

DR. LIPICKY: That may answer the question.

ACTING CHAIRMAN BORER: Okay. I think we can move along to the presentation by Pfizer, the response to ALLHAT. I want to thank you very much, Dr. Cutler. I'm sorry if it seemed like you were being skewered here. That wasn't the intention. This

is a landmark trial, and they are very difficult to do even if they are not landmark. So we're going to -- You know, I think that when the trial is done, there will be a great deal of important information available.

Bob, did you have an additional question? I wasn't going to actually take a break. It says on the agenda that there's a break and, if anybody wants to get up and go out, that's fine. But I think we'll move along.

Pfizer will probably take a minute or two or three getting up here and getting the slides changed, but we'll try and finish the Pfizer presentation before lunch and then go on to the questions after the lunch break.

Pfizer's response to ALLHAT will be presented. Now I'll actually -- I don't seem to have the names written down on my agenda sheet, I'll allow you to introduce all the people on your own.

MS. LOGALBO: Well, good morning. I'd like to thank the panel and the FDA for the opportunity today to review for you the ongoing data that we have accumulated on Cardura, doxazosin mesylate.

This was the slide you were looking for.

I'm Suzanne Logalbo, the team leader for the Regulatory Affairs Group for the men's and women's health products, and I am joined today by Dr. Patricia Walmsley, who is our Senior Medical Director for the doxazosin worldwide team, and Dr. Gretchen Dieck, our senior epidemiologist in our Safety Evaluation and Epidemiology Group.

Our agenda today: We will go through a brief introduction. Dr. Walmsley will then review the clinical data available on doxazosin. Dr. Dieck will then go through our epidemiology and safety evaluation. Dr. Walmsley will return to provide our comments on the preliminary ALLHAT trial observations, and then I will return to take any comments that the panel may have.

We have provided you with a more detailed review of this information in your briefing document which was provided prior to this hearing.

Our objective today would be to review for you the body of evidence that support the conclusions that doxazosin does not precipitate congestive heart failure, and to demonstrate that there is no signal of a causal association between doxazosin and CHF, heart failure-like events, myocardial infarction or stroke.

We believe it is important to begin this

discussion today by reminding the committee of how we came to participate in this hearing. In early 2000, the NHLBI informed us of their decision to discontinue the doxazosin arm in the ALLHAT trial.

We, frankly, we surprised by that action, given the extent of the data that we had on doxazosin through our ongoing safety and efficacy monitoring process. But nonetheless, we were supportive of their decision to act as they believed appropriate in their trial.

What we did with that information is the same process we go through whenever we are presented with new information, and that is that we first asked for clarification from NHLBI on several points that we were looking for further information on, and we began to re-review our accumulated database on doxazosin, beginning with the most rigorous data, that of clinical trials, moving through epidemiology trials, and then finally reviewing our spontaneous adverse event database.

This first assessment was shared with a number of leading cardiovascular experts, and a summary was prepared and finalized in June of 2000. This assessment was shared with key regulatory bodies.

Our conclusion at that time was that

doxazosin does not precipitate congestive heart failure, and there was no causal association with the factors we are talking about today.

We continued to review the data on an ongoing basis through the next year, and when FDA asked us to participate in this hearing, we began to prepare a cumulative review of all the information that we had, and prepared that summary that we've provided to you through February of 2000.

Our conclusions at that point did not change. They remained the same. I would now like to turn the podium over to Dr. Walmsley, who will review our clinical data.

DR. WALMSLEY: Good morning. In this segment of the presentation I am going to go through our clinical trials, which is our most rigorous data. I am going to be -- This is going the wrong way. I am going to be presenting a review of five of doxazosin's clinical trials for selected cardiovascular events. The review will just be a summary of this comprehensive review.

I will then discuss an ongoing NIH trial of doxazosin in benign prostatic hyperplasia, and give a summary of our literature review.

As Suzanne said, in the interest of time,

I am only going to be giving highlights, and the details are in your briefing document.

ACTING CHAIRMAN BORER: Excuse me. Can you move the microphone toward you.

DR. WALMSLEY: Is that better?

ACTING CHAIRMAN BORER: Yes, much better.

DR. WALMSLEY: We reviewed all of our Pfizer-sponsored doxazosin trials with the exclusion of our Phase I studies. That is the studies in healthy volunteers. We looked at trials for both indications, both hypertension and BPH, and also for both formulations. That is the doxazosin standard tablet which is available in the U.S. and the prolonged release doxazosin GITS, the controlled release, which is available in some other countries.

Now ALLHAT was designed to look specifically for cardiovascular endpoints and, of course, our studies were not. So we looked at our studies from a safety perspective, and we focused on specific cardiovascular endpoints -- cardiovascular events, namely, CHF, MI and stroke.

I am going to be focusing on 316 clinical studies, completed clinical studies, including over 49,000 subjects on doxazosin. The vast majority of these were monotherapy studies.

The data from these studies are in two databases. The larger database of 271 completed studies includes the studies from the BPH NDA as well as the studies submitted in the U.K. for approval of the GITS formulation for both hypertension and BPH. The smaller database comprises the 45 studies from the hypertension NDA.

We reviewed both of these databases, and basically the findings from the smaller database were fully consistent with those in the larger database. So we will just be presenting the results from the larger database.

These 271 studies, as I've said, included both hypertension and BPH studies. They included our most rigorous group of studies, 84 comparative studies, 67 of which were cardiovascular and 17 were urologic.

The population of our studies was somewhat different from that in ALLHAT. Patients in ALLHAT, as we have heard, were specifically chosen to be at high risk for cardiovascular disease, and our population is at somewhat lower risk. But our population is probably closer to that in which doxazosin is generally used.

The median age was 55 years, which is

about ten years younger than the ALLHAT population, and in our studies we had a wash-out period before randomization, which ALLHAT did not. Also our studies used the full dosage range of doxazosin.

Another major difference is the duration of the studies. Most of our studies were less than one year in duration, and the vast majority, consisting of about 40,000 of the patients, had a maintenance period between eight and 26 weeks.

Now although this is very short, if you recall the Kaplan-Meier plot for CHF that Dr. Cutler showed, you will recall that the separation was very early in the first few months of the trial, and had this been an adverse effect of doxazosin, I think these studies are long enough to anticipate that this would have shown up in our studies, and it did not.

Here you see the incidence of CHF in our doxazosin patients in comparison with those on pooled comparator. The incidence is very low, and is similar to that on pooled comparator, and there is no evidence of a signal for early CHF events.

Similarly, when we looked for MI and stroke, the incidence of these on doxazosin was very low, and was comparable to that on pooled comparator.

I would now like to look at our 84

comparative studies. Here you see the comparative class of agent, the number of patients on each class, and the percentage of subjects with CHF, MI and stroke.

The percentage incidence of these events in the doxazosin group is very low, much less than one percent, and is, in fact, comparable to that seen in diuretic, which was the comparative agent in ALLHAT, and in the same ballpark as placebo.

When we separate out the 67 cardiovascular comparative studies, we see a very similar pattern, with very low incidence of these events, similar to that seen with diuretic and in the same ballpark. In fact, the incidence is probably similar to what one might expect in this patient population.

These are the 17 studies in BPH and neurology, and again you see a very low incidence of CHF, MI and stroke on doxazosin. It's a little higher than the incidence in the patients in the hypertension studies, but this probably reflects the fact that in the BPH studies the age was on the average about ten years older in the BPH studies.

One of the studies we reviewed specifically looked at doxazosin in patients with congestive heart failure, and this was included in the

NDA filing for hypertension.

We took patients who were still symptomatic from their heart failure, despite treatment with digoxin and diuretics, and randomized them to receive either doxazosin or placebo with a five-week titration period and a 12-week maintenance period, and we saw no evidence of worsening of CHF with doxazosin as add-on therapy in these patients.

In fact, if you look at the number of cardiac events, it is much higher on the placebo arm, significantly higher, with three cases of worsening CHF, two MIs and three sudden deaths in the placebo group, with zero throughout on doxazosin.

When we looked at the other parameters that were evaluated in this study, we see that doxazosin was associated with a significantly higher level of voluntary submaximal exercise. There was a trend to an improvement in left ventricular ejection fraction and a significant reduction in ventricular arrhythmias.

Doxazosin was well tolerated. The side effect profile was consistent with labeling and, in fact, was not significantly different from that in the placebo group. So all the objective parameters in this study showed evidence of improvement.

So based on our evaluation of the Pfizer studies, we showed no evidence of a signal or causal association between doxazosin and the selected cardiovascular events of early CHF, MI or stroke.

I would now like to mention an ongoing NIH trial of doxazosin in benign prostatic hyperplasia. This is the Medical Therapy of Prostate Symptoms trial or MTOPS, and unlike ALLHAT, this is a placebo controlled trial, compares doxazosin and finasteride in men with BPH.

The study started about the same time as ALLHAT, and at the time that the preliminary ALLHAT results were made public, the more than 3,000 patients in MTOPS had all completed a minimum of two years follow-up.

In light of the ALLHAT findings, the MTOPS Steering Committee appointed an independent committee to review the MTOPS data for cardiovascular endpoints, and they found a low absolute risk of CHF and no significant difference in the incidence of CHF among the treatment arms, and no difference between doxazosin and placebo, and they recommended that there be no change to the current MTOPS protocol.

We anticipate getting final results from this study in the coming year, about the same time as

the final ALLHAT results will be available.

We also did a literature review. We had two selection criteria. We looked for longer term clinical trials with doxazosin, one year or longer in duration, and we focused on these, because our own data was from studies less than one year in duration.

We also searched for publications discussing doxazosin and heart failure, and we limited this to patients. We excluded animal studies.

We found 27 publications, including almost 6,000 patients. When we reviewed these, we found no evidence that doxazosin was causally associated with the late occurrence of CHF, MI and stroke.

So in conclusion, we found no evidence of a signal to CHF, MI or stroke in the studies we reviewed. There was no worsening of CHF with doxazosin when used as add-on therapy to digoxin and diuretics in a placebo controlled study in patients with CHF, and interim review of MTOPS showed no significant difference in the incidence of CHF in doxazosin versus placebo arms in men with BPH.

So based on this, our conclusion is that doxazosin does not precipitate CHF.

I would now like to hand over to Dr. Gretchen Dieck, our senior epidemiologist, who will

discuss the nonclinical trial post-approval experience with doxazosin.

ACTING CHAIRMAN BORER: Before you do that, are there any specific questions? Yes?

DR. D'AGOSTINO: The ALLHAT trial has a substantial number of females and a substantial number of blacks involved. These clinical trials that you are summarizing -- how do the composition of male versus female, white versus black compare with ALLHAT?

ACTING CHAIRMAN BORER: Can we turn the microphone on at the Pfizer table, please?

DR. WALMSLEY: I don't have specific numbers, but we did include representative fractions of both sexes and whites and blacks. In fact, if you look in our labeling, there is a statement that it's equally effective in whites and blacks.

ACTING CHAIRMAN BORER: Ileana?

DR. PINA: In your MTOPS data where you have a placebo controlled group, what were the ages of the patients, and was there an exclusion for any evidence of cardiovascular disease or how many of those patients were hypertensive?

DR. WALMSLEY: I'd just like to point out, this is an independent NIH trial. It's not our trial. But the mean age at entry was 63. If you look at the

baseline data, 28 percent, I think, had hypertension in addition to BPH. Eight percent had diabetes, and 19 percent had something which was listed as a cardiac -- something relating to the heart, but it didn't specify what cardiac diagnosis.

DR. PINA: So it sounds like it was a small number of the patients who actually had at least a history of hypertension.

DR. WALMSLEY: Yes, 28 percent.

DR. PINA: Has that smaller subgroup been looked at for the onset or heart failure occurrence in that trial?

DR. WALMSLEY: I don't know, but I think we may have Dr. Kusack here who is the NIH representative for MTOPS. He may be in the audience. He had indicated he would try and come. He may be able to answer that.

DR. PINA: I have one other question. Does Pfizer have any data as to norhormonal levels, renin levels, norepinephrine levels after the initiation of doxazosin therapy?

DR. WALMSLEY: We do have a little data with norepinephrine levels. Dr. Leenen looked at this, actually with prazosin, not with doxazosin, and found some increase. It was also looked at with

doxazosin and was not found, in fact, to show an increase. These were small numbers of patients

DR. PINA: How about renin? Do you have any prazosin data?

DR. WALMSLEY: Renin, I don't know.

ACTING CHAIRMAN BORER: Alan?

DR. HIRSCH: Just to follow up again, what ALLHAT provides is something that doctors kind of enjoy looking at, which is unexpected results in a real-world setting, regardless of mechanism. But to follow up, there's obviously great safety information in your database that you didn't detail. But as you are well aware, the sample is quite distinct. The quality of the endpoints collection is different, and the follow-up is short.

Having said all that, what I would be looking for to follow up on an ALLHAT finding that was unexpected is to try to create a queried subset of the prior data to try to match or case control, in a sense, the ALLHAT population, realizing that it is, in a sense, a special preselected population based on entry criteria.

Instead of looking at the safety of the global Pfizer database, have you made an attempt to try to match or case control your database to match

ALLHAT?

DR. WALMSLEY: I think this is a very good point. I think one of the difficulties is that we have been looking at our safety databases, which don't include all the information, and our databases from the individual studies are individual databases. I think this certainly could be done, but it would take more time than we've had up to now.

I think this, you know, is something perhaps that we should consider.

DR. HIRSCH: I recognize it's very difficult to do, although that would be the analysis I would want to see to try to confirm or refute the findings.

ACTING CHAIRMAN BORER: Michael, did you have -- Okay. Bob?

DR. FENICHEL: The numbers that were presented in your slides are certainly very reassuring, taken on their face. But you get down to the number of cases, you know, I think -- I could be wrong, but I think we're talking about a very small number of cases, perhaps because you were just lucky enough to be in a healthy population.

If you could go back to your slide selected cardiovascular events from 67 comparative

studies, you've got a total of 26 patients on doxazosin and, roughly, I think you had three subjects with CHF in the doxazosin group compared to one subject in the diuretic group out of a total number of diuretics of 483 patients, and so on.

The number of subjects who actually had events seems to be on the order of three or six or six or two or one and so forth. Are there -- Is it your belief that your results are inconsistent with the results suggested by Dr. Cutler? In other words, where do the confidence limits extend?

DR. WALMSLEY: Well, I think that's a difficult answer, because as I explained at the beginning of my presentation, the patient populations are somewhat different. I mean, the ALLHAT patients were selected as being at high risk for these kinds of events, and our patients weren't selected in that way.

We tried to select patients that were more representative of the type of patients that are treated with doxazosin.

ACTING CHAIRMAN BORER: Nonetheless, just to follow up on Bob's point before we move on to another issue, I couldn't do the addition quickly on the slides as you showed them. But in the booklet that we were sent, between pages 16 and 18 there are

a number of tables.

I don't want to make more of these small numbers of events than should be made of them. Nonetheless, can you comment at least, for example, on Table 2 on page 17 where a small but finite percentage of patients on doxazosin had CHF and zero of the placebo did.

It may mean nothing, but when you see that and you hear the hypothesis that would be generated from the unexpected ALLHAT data, you have to ask why is this.

DR. WALMSLEY: You're comparing the 9 with the zero?

ACTING CHAIRMAN BORER: Well, the .17 percent with the zero, yes.

DR. WALMSLEY: Yes. I would like to make a comment here. I am sorry. I presented highlights, and I perhaps should have included a table of just the placebo controlled studies, and you'll find that in Table 6 on page 19.

If you look at the 12 placebo controlled studies, you see that this is zero throughout. I think we can account for this by the fact that when you are doing a placebo controlled study, you really make every effort not to put the patient at risk. So

patients in placebo controlled studies tend to be at lower risk.

Whereas, when we are looking at Table 2, we're including doxazosin patients from all of the comparative studies, including active comparatives which may have been at higher risk.

ACTING CHAIRMAN BORER: Okay. Tom?

DR. FLEMING: I actually had a couple of questions, and I wanted to follow in a similar spirit to what Jeff was just asking, trying to interpret this in the context of what we have from ALLHAT where, with the alpha blocker and the diuretic we're looking at 25,000 people in a blinded, randomized trial that has yielded 1,000 fatal CHD, nonfatal MI events, 600 strokes, and nearly 1,000 heart failure events.

As I probed through all of your data, the two most informative elements that I found were in Section 2, the 84 completed comparative trials, which is the information Jeff was just referring to, that basically gives us in the doxazosin, placebo and diuretic arms ten heart failure events, 26 Mi events, and 23 stroke events, as well as the Section 5 medical literature review.

The essence that I'm struck with here is that these data weren't generated for purposes of

really giving us a reliable estimate of the relative effects on important endpoints such as MI, heart failure and stroke.

There will undoubtedly be in the medical literature review publication bias. There's clearly going to be under-reporting. There's relatively short duration of follow-up. There's a relatively small sample size.

If we took the data that Jeff was just referring to at face value, it would suggest that diuretics may have an adverse effect on strokes and no effect on MIs. Obviously, that's inappropriate, because these are extraordinarily small numbers.

In your view, do these data truly provide us even a glimmer of relevant insight relative to the magnitude of the relevance of ALLHAT?

DR. WALMSLEY: I think you're absolutely right. ALLHAT was the first cardiovascular outcome study that studied doxazosin. What we've done is looked at our database for our most rigorous studies to see what we can find from a safety point of view.

Perhaps after you've heard our comments on ALLHAT, some of our comments on that, perhaps we could take this a little further then.

DR. FLEMING: Okay. I'd be happy to come

back to that then. I did want to, though, ask one more question, because you emphasized this two or three times.

Your conclusion was that available data demonstrate that there is no signal of a causal association for either heart failure, MI or stroke. In essence, are you saying then that doxazosin, in your view, has no effect on those endpoints?

DR. WALMSLEY: I think the early heart failure is the strongest, because based on ALLHAT, we would have expected to have seen an adverse effect, if this was what ALLHAT was showing, in studies of this short duration. I think that is the strongest data.

I agree with you that the MI and stroke, the studies are much too short. But we included them for completion, and we wanted, you know, to review all of our safety data that was relevant.

DR. FLEMING: Is it your intention to establish the conclusion that there is no causal relationship with heart failure, MI or stroke, i.e., that there neither is an adverse effect nor is there a favorable effect?

DR. WALMSLEY: Well, I think what we are saying is we didn't see any evidence of an adverse effect in our database, and there are limitations, as

you've pointed out.

DR. FLEMING: What is the intention of treatment with doxazosin? Is it not, in fact, through effects, in particular reduction of blood pressure, not specifically to reduce blood pressure but mediated through that to achieve beneficial effects on endpoints such as MI, cardiovascular related deaths, strokes and heart failure?

DR. WALMSLEY: Well, that's not just why you use doxazosin. I think that's why you use any drug to lower blood pressure. You are not lowering blood pressure just to lower blood pressure. You are lowering it to reduce the complications of the elevated blood pressure.

DR. FLEMING: And your conclusion is your data, in essence, suggests no evidence of a causal relationship. So if, in fact, there is interest in being able to establish a favorable relationship, you would need to go to other sources of data such as ALLHAT?

DR. WALMSLEY: Yes.

ACTING CHAIRMAN BORER: Steve?

DR. NISSEN: I wonder if Pfizer has any data on peak-to-trough effects for doxazosin at the various doses? Again, I'm trying to understand

relative to the doses used in ALLHAT what -- Blood pressure was measured at a specific time when patients visited the clinic, and I would like to know whether you -- what do you know about peak-to-trough effects at various doses for this drug?

DR. WALMSLEY: Well, I do remember, when we presented this data as part of the NDA, the comment was made by the FDA that this was some of the best peak-to-trough data that they had seen at that point, based on the 24-hour detail. I don't remember the actual figures, I'm afraid. It's ten years ago.

ACTING CHAIRMAN BORER: I'm sorry. Ray? No.

DR. LIPICKY: I have a question that is somewhat like Tom's. Tom, you shouldn't be picking on them. You ought to be picking on us. Right? We usually look at a database of the size that they have -- a tenth of the database, the size that Pfizer just showed, and say we are going to conclude something about safety. So it isn't just their fault.

The question that I wanted to ask was: That placebo controlled trial and the heart failure -- it might be okay for giving some confidence that you don't find some signal, but you must not believe it, because you never pursued it. You don't have an

indication for heart failure. What happened?

DR. WALMSLEY: Well, this was done a long time ago, and the ACE inhibitors have since been approved for heart failure and shown to be very effective. I mean, at the time, really, people were looking for something to help digitalis and diuretics work in patients who were still symptomatic, and they were looking at the addition of vasodilators, and this is why we tested this. But --

DR. LIPICKY: Okay.

DR. WALMSLEY: -- it really showed that there was no harmful effects, but I don't think it really showed enough benefit to make us pursue this as a CHF indication.

ACTING CHAIRMAN BORER: Why don't we move ahead then -- Thank you very much -- to Dr. Dieck, and we will hear the next part of the Pfizer presentation.

DR. DIECK: Thank you. I would like to continue our discussion in decreasing order of scientific rigor. I would like to describe the results of an epidemiologic study that had been carried out in the early Nineties, and I would also like to review our spontaneous reporting experience.

Prescription event monitoring, or PEM, is an epidemiologic technique that was developed by the

Drug Safety Research Unit in the U.K. PEM is generally carried out -- or it's a means of being able to identify a cohort of patients using prescriptions and follow them for several months for their adverse experiences.

Typically, in the U.K. PEM is carried out shortly after a product's launch, and approximately 8-12,000 prescriptions are identified from the prescription pricing authority. The prescribing physician then sends out what are known as green cards on a monthly basis to the patients, and they in return fill out the form with adverse experiences they may have had, self-reported, and send them back to the Drug Safety Research Unit.

For doxazosin approximately 8500 patients were identified from March of 1989 through January of 1991, and the report from the Drug Safety Research Unit identified that event rates for cardiac failure, cerebral vascular accident and ischemic heart disease, again self-reported diagnoses, were consistent with those observed for other PEM studies of antihypertensive agents.

We can see this on the next slide. These are the first month's results, but the report also concludes that the average of months two through six

had similar types of results.

Here we have the event rates for doxazosin compared to other antihypertensive agents, and there is no signal here that these events are being reported with greater frequency for doxazosin than these other drugs.

I would now like to review our spontaneous reporting information for completeness, and our safety alert database is comprised of spontaneous cases reported to Pfizer by medical professionals and consumers, by the medical literature and also by other adverse events registries.

It is important to keep several things in mind when interpreting spontaneous reported information. First, it is important to note that it is anecdotal in nature and, whereas the clinical trials in epidemiology are carried out in a scientific or quantitative framework, that's not the case with spontaneous reports.

The reporting rates themselves are a function of a variety of external factors such as the indication of the drug or the drug itself with immediate exposure and regulatory actions and so forth.

Most importantly, the spontaneous

reporting information provides us with a reporting rate, but this is no means an incidence rates.

We review our spontaneous reporting data on an ongoing basis, and what Ill show you are the cumulative results of our February -- cumulative through February 2001. I want you to keep in mind that these results are in the universe of 4.1 billion patient days of therapy for over 13 years of worldwide experience with doxazosin.

Our safety review of events of heart failure-like events, stroke-like events, myocardial infarction or related events were similar as those and consistent with those generally seen for these types of agents.

Here we've compared -- This is a reporting rate percentage over all cases reported, and we are comparing doxazosin to amlodipine, glipizide and nifedipine. Glipizide is a sulfonurea, but it was used in a similar patient age and sex population as the other drugs.

Here again we have reporting rates for heart failure-like events, myocardial infarction, related events, and stroke-like events. We are simply stating here that there was no signal in our continuous review of the spontaneous reporting system

that these events were being reported at a higher rate with doxazosin than similar types of drugs.

I would now like to hand the podium back to Pat Walmsley so she can discuss Pfizer's comments on ALLHAT.

DR. WALMSLEY: Thank you. I would now like to present Pfizer's comments on ALLHAT, although many of these have already been touched on.

I first of all wanted to remind you that the primary endpoint of ALLHAT, fatal coronary heart disease and non-fatal MI, showed no difference between doxazosin and chlorthalidone, and this was despite a two to three millimeter difference in systolic blood pressure.

We feel that additional information is essentially to fully interpret the study findings. We would like to know the details of therapy, dose and blood pressure for all the blood pressure with CHF and stroke events.

Although intention-to-treat analysis is the normal way to analyze these large trials, we feel that in this instance an on-treatment analysis would help to clarify the relationship of therapy to events, in view of the fact that at one year almost one patient in five in the doxazosin group was not taking

his assigned medication, and this increased to one patient in four by four years.

We feel that, to make an assessment of the relationship between events and therapy with a view to looking at this from the safety aspect, we really need to look at the patients who were actually taking the drug.

We would like to know the mean dose of doxazosin in the patient population in order to relate this to blood pressure control, and we also would like to suggest an analysis of those patients who reach blood pressure goal versus those who did not to help determine the relationship of event to class of therapy. There was, in fact, a difference in systolic blood pressure reduction in the two arms.

I would now like to look at the secondary endpoint of congestive heart failure that was the one causing the most concern. As the paper discussed and as you have head, other secondary endpoints, stroke and angina, in fact, were attributed by the authors to possibly being -- probably being related to the difference in systolic blood pressure.

Now here, as you've seen, there is a dramatic and very early separation of the curves in the first year, with maximal separation occurring by

the first year. This raises the question of the role of discontinuation of prior therapy.

We know that 90 percent of the patients were taking prior therapy. We don't know what this was, but just based on general prescribing patterns in the U.S., we can assume that many of these would have been on the diuretic or an ACE inhibitor.

We know that these patients were at high risk for developing CHF. They were older. Forty-five percent of them had atherosclerotic cardiovascular disease at baseline. About a third were diabetic. Sixteen percent had LVH, and it's likely that some of these at entry may have had latent CHF that was being treated by their diuretic.

When this diuretic was stopped and doxazosin substituted, doxazosin, of course, being a drug that is not used to treat heart failure and, moreover, in some patients can cause some fluid retention, it's likely that this latent CHF would have become manifest and been diagnosed as an event. This, of course, wouldn't have happened in the group where you are discontinuing diuretic and replacing it with another diuretic.

Latent CHF is difficult to diagnose in this primary care setting without a sophisticated

cardiovascular workup. And as we've already said, chlorthalidone is an effective treatment to CHF, and doxazosin is not.

CHF is a complex syndrome with a high mortality rate, and we have already seen the all-cause mortality slide which shows no difference between doxazosin and chlorthalidone. This lack of a difference in all-cause mortality is difficult to understand in view of the difference observed in CHF incidence.

As ALLHAT had no placebo group, as the authors pointed out in the paper, we cannot say whether the incidence of CHF is increased on doxazosin or decreased on chlorthalidone, although studies such as the SHEP trial indicate that it may possibly have been more related to the latter, and this was, in fact, discussed in the ALLHAT paper.

If we look at SHEP, the Systolic Hypertension in the Elderly Program, this is an NHLBI study that was first reported about ten years ago. It included over 4,700 patients over 60 years of age with isolated systolic hypertension, and it compared chlorthalidone with placebo.

The follow-up was a little longer than ALLHAT, 4.5 years versus 3.3, but like ALLHAT heart

failure was a secondary endpoint. Moreover, the diagnosis of CHF, the criteria for diagnosis of CHF in ALLHAT were based on those in SHEP.

Now when we compare the incidence of CHF in SHEP versus ALLHAT, you see the percentage incidence of CHF on placebo compared with diuretic in SHEP. There's a difference of a factor of approximately two. When you look at the ALLHAT data, we see the same ratio between the incidence of CHF on doxazosin versus diuretic as we do in SHEP in placebo versus diuretic.

This seems to suggest that possibly the relative difference that is seen in CHF in ALLHAT may be more representative of the beneficial effect of the diuretic on CHF than an adverse effect of doxazosin. In other words, the doxazosin is behaving like the placebo group with regard to CHF with no benefit and no adverse impact.

We have already touched a little on this, but in studies such as ALLHAT, in many studies, there are practical considerations which prevent the optimal usage of the drug. There are limitations that are based on things like the need to blind the drug and also the need to standardize visit intervals, etcetera, which mean that you can't always use the

drug in the way that it would be used as labeled.

Perhaps a drug like doxazosin is at a bigger disadvantage here, because doxazosin has five different dosage levels. So it's difficult to blind against an agent that has two or three dosage levels.

So one has to accept limitations, and this meant that there was a slower titration to a less than maximum dose with doxazosin, the maximum in the trial being eight versus 16 in the labeling, and this may have impacted on blood pressure control and event rate in the early months, particularly in vulnerable patients.

If you look at the mean systolic blood pressure results, although the mean systolic for doxazosin is below the goal of 140 for most of the trial, you see that it takes longer to reach that goal. In fact, it is about 12 months before we are actually at that goal. Whereas, with chlorthalidone we get to the goal at somewhere round about four months.

This means, as these are only means, that the outliers -- that there would probably have been many more patients with systolic well above goal.

Finally, we would like to remind everyone that the ALLHAT are preliminary data, and there are

many questions that remain before the full implications of the study can be understood. We would like to reiterate that we would like an on-treatment analysis to fully interpret the results.

Our overall conclusions are that doxazosin doesn't cause CHF, as seen in our review of our clinical studies, literature review, the post-marketing studies, and spontaneous reporting.

We would like to emphasize that ALLHAT documented a relative difference in incidence of CHF. It didn't demonstrate causality, and there are several factors which may have contributed to this relative difference, the most important probably being that chlorthalidone is an effective drug in the treatment of CHF, and this is supported by SHEP, as I showed you.

Many of the CHF events were early, and discontinuation of prior therapy with diuretics and ACE inhibitors may have played a role, as may the fact that doxazosin, as we have discussed, was not able to be used to optimal efficacy.

I would now like to hand back to Suzanne LoGalbo for some closing comments.

DR. D'AGOSTINO: We've heard a number of times that the separation between the two drugs is

early, and that somehow or other is interpreted that, if you explain the early separation, you're fine. But if you look at the graph of the congestive heart failure -- and I'd like Tom's comment on this also -- it's consistently a relative risk of about 2, no matter what year you're going through.

We have a longer follow-up. We have more individuals in the follow-up at one year, but it isn't that it only happened at one year and then it pulls together. It's consistently a relative risk of 2 across the board. So it's more than just a quick effect of the congestive heart failure showing itself.

ACTING CHAIRMAN BORER: Can we have the mike on at the table, please?

DR. WALMSLEY: I think that's true. There is, obviously, more than one factor here, and I think the role of discontinuation, together with the fact that doxazosin wasn't used at its optimal dose, may well have played a role in the early cases of CHF and, as you said, there is a slight continuing divergence total time, but we are comparing --

DR. D'AGOSTINO: Yes. It's not slight. It's consistent.

DR. WALMSLEY: We are comparing an agent that treats CHF with one that doesn't treat CHF, and

it may be that some of the patients on chlorthalidone, in actual fact, would be developing CHF if they weren't on treatment, that it's already controlled and, therefore, not diagnosed.

DR. D'AGOSTINO: I have another question which may be unfair, but let me ask it.

You raise the question that maybe it's a beneficial effect of diuretics as opposed to a negative effect of Cardura. Does that mean that ALLHAT should have continued with the arm? If that is true, should ALLHAT have continued with the arm?

I mean, say the separation is real and we believe it, and we say, well, we shouldn't worry about it, because it's just that the diuretics were a lot better for CHF, so let's continue on.

DR. WALMSLEY: Well, we haven't seen all of the data, and we certainly haven't seen the data that the people who made this decision have seen. I think we felt we should support their decision, because it's their study, and they have seen the data, and we would support them.

I think it's a hard question to answer when one hasn't seen what they saw.

ACTING CHAIRMAN BORER: Tom and then Ileana and Ray.

DR. FLEMING; I'd like to get to Ralph's question as well, following up on that. But two other real quick preliminary issues.

You had raised what you were suggesting was maybe an inconsistency between the difference in CHF without the difference in mortality. But the difference in CHF was a 4.4 versus 8.1 percent occurrence or about a 3.7 percent excess; whereas, mortality estimates were about 9.08 and 9.62.

So in essence, is it that inconsistent to say that, if there are 3.6 percent more cases of heart failure, that may translate into .6 percent more deaths?

DR. WALMSLEY: I don't know. I'd like to ask someone with more statistical experience than I have.

DR. FLEMING: Okay. Well, I'll just go on to say it's not so obvious to me that that is inconsistent.

The second point: You noted that there was, in fact, this titration schedule that led to a potential delay in getting to more optimal doses. That would -- or ore optimal dose levels, and that may, in fact, in particular, influence stroke rate, I would think. Yet there were no difference in stroke

rates over the first nine months.

So is it, in fact, plausible that it was the titration schedule that really accounted for an apparently unfavorable effect of doxazosin?

DR. WALMSLEY: I guess I was just trying to explain all the possible reasons that we could think of that might account for it, and there's no doubt that the blood pressure was less more controlled in the first year, and there's no doubt that patients weren't on an optimum dose.

If you look at the paper, I think 37 percent of the patients were on less than 8 milligrams at one year, of doxazosin.

DR. FLEMING: Let me move to the third question, which is somewhat related to Ralph's.

Your general sense in interpreting the data is that doxazosin didn't harm the occurrence of a risk of heart failure, but rather the diuretics provided benefit, and you drew that conclusion by looking not only at the results of ALLHAT but also SHEP.

I actually tend to agree with you. That's my interpretation as well. These data would suggest that diuretics are particularly effective in reducing risk of heart failure and, when you put the data

together from the two studies, it would suggest that doxazosin is neither harmful nor at all beneficial.

Granting then your conclusions, you then go on to look at the primary endpoint of fatal CHD and non-fatal MI, noting no difference. In a certain sense, I interpreted you were looking at that in a favorable way.

Why is it favorable? If we're comparing to an alternative control that we've granted is much more effective on an endpoint as important as heart failure, why is it okay to just be the same then on cardiovascular deaths and non-fatal MIs?

DR. WALMSLEY: Well, I was trying to point out that there was no difference, that we were no better, but we were no worse.

DR. FLEMING: And is that a good thing or a bad thing?

DR. WALMSLEY: Well, I certainly don't think it's a bad thing, but I'm not a statistician.

DR. FLEMING: Well, this isn't statistical. This is clinical. If we grant your statement that the diuretic control regiment is unequivocally better in treating heart failure, then why is it adequate when you are comparing to that comparator to be the same on cardiovascular related

deaths and MI? Shouldn't there in some sense be an area where you would hope the experimental therapy is better then?

DR. WALMSLEY: Yes, I think you're right. I mean, we had hoped that we would show superiority when we entered the trial.

ACTING CHAIRMAN BORER: We have Ileana and then Ray.

DR. PINA: Yes. I wanted one question to follow up my previous question, and then a clarification.

You made a statement that doxazosin makes retention of fluid, and I had asked you before if you knew what happened to things like renin level and other neurohormonal levels with the drug. What do you postulate is the mechanism of fluid retention in this type of agent?

DR. WALMSLEY: Many vasodilators do cause some elements of fluid retention, and I don't know that the mechanism has really been fully worked out.

DR. PINA: Some vasodilators cause edema, not necessarily true fluid retention, which may be two different things.

My second point is a clarification. Chlorthalidone is not a commonly used diuretic at all

in heart failure patients, and it's a difference between congestion and heart failure, and they are two different things. All heart failure patients are not congested.

I tend to agree with you that something got unmasked, because it happened very early. So I agree with Dr. Fleming's point, but that fluid retention somewhere in there needs to be explained.

ACTING CHAIRMAN BORER: Ray?

DR. LIPICKY: Well, I just wanted to reiterate, because I think it got forgotten and I'm not sure it's right, that the distinction between -- that somehow or another one needs to make the distinction here for congestive heart failure whether irreversible harm occurred; because if this is just reports of heart failure, then in fact that's a different thing from heart failure occurring as a progression of disease.

I repeat the statement that the two groups may have had heart failure progressing equivalently, but that one group would have had more reports of heart failure, because in fact they weren't receiving a diuretic. So that that distinction, I think, is important to make, and particularly when we get to it this afternoon, since this is a drug indicated for

benign prostatic hypertrophy.

If you think that there is, in fact, some effect of doxazosin on the heart that causes heart failure, then people with BPH shouldn't be receiving it either. So this is a subtle distinction that, I think, needs to somehow or another be debated.

ACTING CHAIRMAN BORER: Marvin?

DR. KONSTAM: Can I just add one other point to that, Ray. I mean, we talked about the potential effect of the diuretic, but there's also a potential effect of the blood pressure difference that may not be directly linked to irreparable harm, and that is to say that, if your blood pressure is higher, your afterload is higher, and you are more likely to present with heart failure, independent of whether that has any significance with regard to natural history and irreparable harm.

So there are a couple of things going on early on. One could be the diuretic effect -- you know, as has been pointed out, not only the 3 millimeter difference but the year that it took to get to below 140 in the mean. So that could be also influencing people coming into the hospital with heart failure.

DR. TEMPLE: Let's suppose it's really

true that -- not that it's easy to know this -- that doxazosin doesn't actually make you get heart failure, but it's merely not a drug that treats it. It's suppose that's true for the moment.

What do you feel the proper role in therapy is for a role like that when a lot of people, it turns out, not known to have heart failure before they entered the study turn out to be at high risk of heart failure, and the consequence of using doxazosin instead of something else -- we all wish we knew what the other drugs in ALLHAT had been doing in this case, but we don't. What's the implication of that for first line versus second line therapy, whatever the explanation.

Maybe it's even that it takes longer to get to goal. Whatever the explanation, doesn't that suggest that it's not a very smart first line drug, as other people have suggested? How do you all feel about that?

ACTING CHAIRMAN BORER: Can we turn on the mike at the table, please?

DR. WALMSLEY: ALLHAT was a high risk population, and I think when you are looking at patients who are at lower risk, particularly at lower risk of developing heart failure, doxazosin can be a

very useful drug, particularly --

DR. TEMPLE: Take for a moment the SHEP population. I don't know whether that's very high risk or not, but the benefit of a diuretic compared to a drug -- that is, placebo -- with no effect on heart failure was apparently obvious there also.

So let's say doxazosin just has no beneficial effect on heart failure, but is here neutral. So that's another place in which there seems to be some benefit, not necessariliy that that affects survival, but hospitalization isn't good, and heart failure symptoms aren't good. Why would one do that?

I'm trying to take your best case assumption and follow up what the implications of it are.

DR. WALMSLEY: I think most people these days seem to feel that the most important thing is to get the blood pressure under control, and if you are giving a drug like doxazosin, whether you are giving it first line or as add-on, you need to get the blood pressure under control. If the blood pressure isn't controlled, you need to give something else with it.

I think in patients who have mild hypertension and low risk, and particularly patients, for instance, who have mild hypertension and BPH, it's

very useful as initial therapy. But I think it's very important to make sure that the patients don't have any increased risk for CHF and that they do get to goal.

DR. KONSTAM: Can I ask you a question, Dr. Walmsley? Can you tell us something about how doxazosin is used in the community? You know, how often are doses above 8 milligrams used? How different is ALLHAT from -- I understand the packet insert, but in terms of actual use?

DR. WALMSLEY: Well, I think this is an interesting question, because if you look at our studies that we've done, the mean daily dose for efficacy is close to 8, just under 8. But if you look at the real-world population, most physicians don't titrate it that far.

I think this is one of the problems with our standard doxazosin formulation, because if you start with an effective dose, you might get an excessive hypotensive response. We start with a dose 1 milligram and titrate up, and very few patients will respond to 1 milligram, and 2 milligram is not a great deal better.

So physicians don't tend to like to keep titrating, and they get fed up and switch.

DR. KONSTAM: Well, so just to go with that for a second -- I mean, you've raised some important points about needing to know more about the doses used in ALLHAT -- actually used in ALLHAT. But let's say for the sake of argument we find that it isn't that different from what's going on in the community.

Then we say, well, part of the difference in the events may be a function of less effective blood pressure control in the doxazosin arm. What conclusion would you draw from that? Would you say that something has to change in terms of educating practitioners on how to use doxazosin or what conclusion would you draw from that?

DR. WALMSLEY: Well, I think there is another difference in ALLHAT. Again, because of the design of the study, that means doxazosin isn't used typically in the way it's used in the community, and that is the choice of additional therapy to get to goal.

I think very few physicians would add to an alpha-blocker reserpine, hydralazine, fonadine. I think the usage --

DR. KONSTAM: But it sounds like that's not actually what was added most of the time in

ALLHAT. Right? It was beta-blocker most of the time.

DR. WALMSLEY: Well, beta-blocker was the most frequent, but if you add up the incidence of the others -- I don't know the data, but from the paper it looks as if there were a significant number of patients who received the others.

I think in the clinic situation most physicians, if they are using something in combination with doxazosin, would probably choose either a diuretic or an ACE inhibitor or calcium blocker rather than one of the other agents.

ACTING CHAIRMAN BORER: Ray?

DR. LIPICKY: You left the topic of which is better too soon for me. If I were a practicing physician, and I'm not and haven't been in sometime, I would prefer to use doxazosin if I knew that it didn't cause heart failure; because I want to know when my patients are developing myocardial problems, and I want to be aware of that, because that definitively changes their prognosis, and I want to tell them to get their lives in order.

I do not want to mask the symptoms of heart failure and, therefore, delude both the patient and myself. So I would suggest that there isn't any clear answer to which is better. It depends on the

circumstances, and that I don't know which is going on here.

ACTING CHAIRMAN BORER: Okay. I think we are getting into the discussion of the questions here, and rather than do that, maybe we can let Pfizer complete its presentation, and then everybody who wants to can go to lunch.

I want to point out while you are coming up here that we don't take breaks, because the United States government expects us to give a full day's work for a full day's pay here or, in the case of this committee, a full day's work for no pay, and we're going to do that.

MS. LOGALBO: Okay. I just want to quickly just answer one of the questions. About 70 percent of the use in the U.S. is add-on therapy on doxazosin.

I would like to indulge the committee for a second and introduce Dr. Sverre Kjeldsen, who is the Chief Cardiologist at the Ullevaal University Hospital in Oslo. He has some comments on the trial design which might be helpful in coming to some conclusions before we move on.

He does have some overheads. Is there a way to have the screen brought down and the overhead

turned on?

DR. KJELDSEN: Committee members, ladies and gentlemen, is it possible for me to show some few slides?

ACTING CHAIRMAN BORER: Can we have some audiovisual help to get the overhead back?

DR. KJELDSEN: I am a practicing cardiologist based on the University Hospital in Oslo, and I am invited here because I am heavily involved in clinical trials, outcome trials in hypertension, and I am currently involved in leadership of studies comprising about 45,000 hypertensives, including the VALUE trial supported by Novartis, the LIFE study supported by Life, and the ASCOT trial which is supported by Pfizer.

In the ASCOT trial in U.K. and Scandinavia, we have randomized 19,000 hypertensives at very high risk comparing outcome on atenolol and amlodipine, and in that trial we use doxazosin as add-on treatment, and we have decided not to make any changes in that.

I just want to make some few comments on the ALLHAT population. First of all, this is taken from the publication. We see that it's a very high risk population, high age 67. Ninety percent were

previously treated with probably two drugs. Could be diuretics, beta-blockers, ACE inhibitors. About half of these subjects had coronary heart disease. Twenty percent had LVH, and a third of them qualified into the trial with diabetes.

So it's very likely that a lot of these subjects really had latent heart failure. This is not really a primary prevention study. To me, it seems to be much like a secondary prevention study.

Elderly subjects: Very high risk of heart failure, and then previous medication is discontinued. I mean, medication including probably diuretics and ACE inhibitors treating heart failure, and then these subjects are rolled over onto either something that is treatment for heart failure, chlorthalidone, or something which is insufficient dose of an antihypertensive agent like doxazosin.

Whether this is true heart failure or just fluid retention cannot be decided, because we haven't seen the data. But the curve really suggests when they separate very early on that much of this could just be explained by fluid retention in subjects predisposed to having heart failure. And there is a slightly separation on, which could possibly be explained by new cases of heart failure, probably then

caused by difference in blood pressure.

This is taken from a previous review of 12 clinical trials based on diuretics, comparing placebo. Heart failure was reduced by about 50 percent. It suggests that if doxazosin -- in the worst scenario, doxazosin is neutral. It's like placebo.

If in case one claimed that doxazosin is causing heart failure, it should be causing a deadly disease. But mortality, as we have seen now repeatedly, is completely unchanged between doxazosin and chlorthalidone.

Just wanted also to emphasize on the primary outcome: Coronary heart disease is probably the main reason for heart failure, and there is no difference between doxazosin and chlorthalidone in the ALLHAT trial. This is the primary endpoint the trial was designed to investigate.

This is quite interesting, even in light of the difference in blood pressure. Despite the fact that blood pressure has not been properly treated in the doxazosin arm, the outcome, the primary outcome is identical. No difference in coronary heart disease between the two groups.

So putting it altogether, comparing the ALLHAT data with data from other large clinical

trials, comparing different antihypertensives during the recent years, there is really no difference if you just focus on the primary endpoint.

I think we should focus on the primary endpoint in these trials. That's what they have been designed to investigate, and current knowledge in the treatment of hypertension says that it's the blood pressure lowering effect per se which we should go for, and that all these drugs actually are equal in preventing the primary endpoint. Thank you.

ACTING CHAIRMAN BORER: Okay. Are there any other comments from Pfizer?

MS. LOGALBO: Just the one that we wanted to leave you with before you go to lunch. In essence, it's what we have been saying for most of the morning, that based on the totality of the data that we have reviewed over the time that these findings have been found, that we know that doxazosin does not precipitate CHF, and that our recommendation at this time is that there is no action that is required and that, if diligent monitoring should be continued and if in the future there are further findings that more elucidate these results, we would be happy to work with regulators on an ongoing basis.

Thank you very much for your time, and I'm

sure we would want to make some closing remarks before we go to lunch. Thank you.

ACTING CHAIRMAN BORER: Thank you very much. I really want to thank all the formal presenters. This is a very serious question or series of questions that are being raised here, and we will go over them preliminarily after lunch before getting into the particular issued raised by the FDA. But we have heard a tremendous amount of information presented in concise and clear fashion, and I want to thank everybody who has done that.

We are going to break now for lunch. It's important, if you intend to do that, to know that the NIH no longer has a cafeteria in its basement. If you haven't been here in a while, that's going to come as a surprise.

It is on the second floor. So you can go out to the second floor, have lunch, and we'll come back here and begin no latter than 1:15.

(Whereupon, the foregoing matter went off the record at 12:12 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:16 p.m.)

ACTING CHAIRMAN BORER: Do we have the Committee members in the room? While we are all getting together, it may be useful to make a couple of short points.

First of all, it would be unfortunate if, in the discussion this morning, a few facts were forgotten. Number one, that it's virtually impossible to answer all the questions you want to ask in a single clinical trial. So it's not surprising that many of the issues about which Dr. Cutler was asked couldn't be fully answered in a rigorous way. You just can't do that with one single trial, and this was an outstanding trial, but it's just one trial.

Important information on specific points can be obtained, and the citizens' petition suggests that sufficient information has been obtained thus far from this trial to support changes in the instructions for use of the drug, and the FDA has asked us whether we, the Committee, agree with that.

We are going to go over the specific questions that the FDA asked the Committee this afternoon. They fall into three categories, I think, or two with a subset, and I believe it's useful to

keep these in mind as we go through these.

First, not in this order necessarily: Is labeling needed? We heard a fair amount of discussion about this just before lunch. Is a labeling change needed if one antihypertensive drug doesn't provide all the benefits of blood pressure reduction that are expected and seen with all other drugs? That's one issue.

That is separate from the issue of whether the data we have been presented indicates that the drug in question here doesn't provide these benefits, given the issues of dose, time and all the issues that were raised.

Then as a subset of that second issue, we have to decide whether or not this drug, doxazosin, causes irreversible myocardial dysfunction or damage or whether it allows irreversible myocardial dysfunction to happen that wouldn't have happened if a different drug were used or dysfunction that wouldn't have occurred if another drug had been used.

Those are the things that we are really being asked to respond to. Those are the issues we are being asked to respond to, but we are being asked in a program fashion with several questions.

Our reviewer for the Committee is Tom

Fleming, and before we go through the questions, which we will do in structured format and may have questions for the formal presenters while we are doing that, it would be useful to hear Tom's overview, since he is the reviewer for the Committee and has some specific comments to make.

DR. FLEMING: Thanks, Jeff. There's obviously a myriad of complex issues here and several pages of questions, and what I will try to do is try to give a quick overview and summary, focusing more on specific data and preliminary or first line interpretation of that data, and assume that we will get into much more details as the discussion goes on.

Essentially, I've organized my summary thoughts in the context of, first, looking at the data presented to us by Pfizer, then touching on the ALLHAT data, and then SHEP, and then some summary thoughts.

Pfizer's presentation was based on their review of available clinical and post-marketing data on doxazosin, and they focused on heart failure, MI and stroke, and in essence have provided in Sections 2 through 5 of their report information on overall trials, their early alert safety database, their prescription event monitoring, and their medical literature review.

In essence, in my review the data that really was potentially most informative came from their Section 2 comparative trials in which there were 271 and 47,000 participants. In particular, I focused on the 84 completed comparative trials, 67 of which were in hypertension involving about 5,000 patients receiving doxazosin and 1600 on placebo, and about 500 on diuretics.

As I had mentioned this morning, what certainly stands out is that that information in terms of heart failure, MIs and strokes are really very limited compared to what we learn from ALLHAT with 10, 26 and 23 respectively events in total on those three arms, compared to roughly 1,000, 1,000 and 600 heart failure, MI and stroke events that we see from ALLHAT.

In addition, the source of information here, obviously, is going to have -- because of its nature as a safety database, in particular, is going to be looking at much shorter duration, smaller sample sizes and under-reporting. In fact, that database would suggest that, if you took literally what the results show, that diuretics themselves don't provide favorable benefits on heart failure, MI and stroke; and obviously, that would be very misleading to conclude that in those small numbers.

In their medical literature review in Section 5, the biggest source of data in those 5900 subjects came from 4200 subjects in a surveillance trial in Norway, and again in a surveillance study such as this one has to be incredibly cautious about publication bias, under-reporting, relatively short duration, follow-up, and small sample sizes.

It was noteworthy, though, that in that experience HDL cholesterol levels did seem to fall, which they had noted as one surprising observation.

Overall, the sponsor concluded in their review of all of this information that there was no signal regarding a causal relationship between doxazosin and heart failure, MI and stroke.

My own sense is that such surveillance data certainly do play a role, and this type of information would be very informative in detecting safety events that occur with a very high relative risk.

Essentially, though, if we are trying to use these data to generate some relevant and informative insight in the context of the ALLHAT data, I see that this information is not particularly additively informative in the sense that it is not going to be effective in detecting increases in

adverse events where the relative risks are less than or equal to two, which is what we are looking at here in ALLHAT, as well as being able to really address longer term effects, where many of these sources of information were for very short periods of time for treatment, on the order of one month.

ALLHAT then presents for us an incredibly important resource for understanding relative efficacy on primary and secondary endpoints and in safety measures.

Based on what the protocol had indicated, as well as where the focus has been by the study team, the primary endpoint is fatal CHD and non-fatal MI, which clearly are critically important outcomes. When one looks at other clinically compelling or very important outcomes, certainly stroke and heart failure are key.

So from a statistical perspective, even though outcomes that address effects on stroke and heart failure are secondary endpoints, they clearly stand out as especially important, clinically important endpoints.

What we've seen, as has been discussed at length, is an increase in the rates of all of these endpoints on the doxazosin intervention, although for

the primary endpoint the increased relative risk is very close to one, 1.03.

Pfizer has raised several important concerns about the interpretation of ALLHAT. I'll just quickly pass through them, because these will certainly be important in our discussion today.

One is whether or not the titration schedule and maximum dose contributed to a less than optimal blood pressure management, and one of the issues that we need to address is: Nevertheless, is this schedule and dose used in ALLHAT in essence consistent with what is a real-world schedule?

Marv was in essence probing a very important issue, and that is does this match what people do in the real world? How often do people get to 16?

Certainly, one of the major issues that one would raise with a less than optimal blood pressure control, in particular, would be less than optimal control for stroke. It's noteworthy that the diastolic outcomes, though, were the same between the diuretics and the alpha blocker. The systolic differed by 3 millimeters at one year and 2 thereafter.

It was of interest, though, in my review

of the data that stroke differences that emerged, emerged after nine months. There were no differences in the first nine months, and the stroke differences at two years were only a third of the overall stroke differences seen at four years.

So where the differences in blood pressure between the alpha blocker and the diuretic were most apparent in the first year, over the first two years the excess stroke rate was half of what the excess stroke rate was between years two and four.

The sponsor has also pointed out that there is a need for additional data that's not yet been presented by the publication. Certainly, that is an important issue. We have only received what we have been provided in the main publication of this study, and there are many additional important analyses that aren't yet possible, based on the data that have been presented.

One of those sets of analyses that have been asked for are on-treatment analyses and analyses of patients who actually reached their blood pressure goals. Being an intent-to-treat enthusiast as I am, I would argue, though, that even though those could be of some merit as supportive analyses, the most interpretable analysis is the analysis that was

presented to us in the manuscript, the ITT analysis.

One is always left, for example, when you are looking at subgroups of people that, for example, met their blood pressure goals, of sorting out what, in fact, represent a treatment effect versus what are the intrinsic characteristics that define patients who could reach those goals versus those who couldn't, and that confounding forever leaves those kinds of analyses, beyond treatment analyses and the analyses of people who reach targeted goals, as very difficult to interpret.

The sponsor, Pfizer, also noted that there was an early emerging difference in heart failure, and the overall doubling in heart failure seems to be inconsistent with the lack of mortality differences. In fact, Ray has raised the question: Is, in fact, the heart failure effect really an unmasking effect that we are seeing?

It's difficult from my perspective statistically to sort that out. The excess in heart failure is 4.5 percent versus 8.1 or about 3.6 percent overall, and there is a .6 percent difference in mortality at four years.

It may be, if one followed for a longer period of time, that additional differences may

emerge. That's, in fact, one of the important additional insights that may, in fact, come from more complete data.

The sponsor made one other key point, and that was that the diuretics regimen does decrease heart failure by a factor of about two, if you go back to the SHEP data. In turn, if you use ALLHAT, diuretics reduce heart failure by a factor of two relative to the alpha blocker, leading them to conclude that, in fact, the alpha blocker is probably the -- is inert, neither favorable nor unfavorable.

I find that a fairly strong argument. In fact, it draws my attention to the SHEP data. In fact, going to the SHEP data, one of the issues that I think is extremely important for us to address is what nature of effect does one need to see on the primary endpoint, in particular, but also on secondary endpoints, to conclude that doxazosin, in fact, is beneficial?

The Data Monitoring Committee and the Steering Committee recommended termination of the study, in essence based on what I would call a superiority analysis, i.e., the data reflected little difference on the primary endpoint between doxazosin and diuretics.

Conditionally given the analyses that had been observed in that 60 percent of projected events, the calculation was there was only a very small probability of superiority being seen on the primary endpoint in the final analysis. Roughly less than one percent, I think, was that analysis.

To justify termination then based on a low likelihood of a positive result, it is implicit then that no difference is unacceptable. In essence, as I interpret what the Data Safety Monitoring Board and Steering Committee has judged, is with compelling evidence of lesser benefit on heart failure and other considerations such as cost, that if doxazosin, in fact, yields only the same result as diuretics on the primary endpoint of fatal CHD and non-fatal MI, then that's an unacceptable effect.

That's an issue that I think deserves some considerable discussion by us this afternoon. I would like to maybe add a little bit of insight before we get into that discussion.

An alternative approach, an alternative interpretation of these data would be to say SHEP established diuretics to be effective. If, in fact, we can show alternative regiments are equally effective, then that in essence leads to the

conclusion that we have an intervention that, in fact, is better than placebo. That's the classical noninferiority argument.

So the question might be raised: Even though I believe the protocol team clearly provided strong evidence that, if ALLHAT were to continue to its full completion, the probability of being able to show superiority of the alpha blocker to the diuretics was very low, which I believe is established, can one at least conclude that the alpha blocker has a beneficial effect on fatal CHD and non-fatal MI?

To address this, essentially I used two sources of information, SHEP to give me the active comparator effect, and ALLHAT to give me the relative effect of the alpha blocker against the diuretic.

In essence, I did this quick analysis on heart failure, stroke and the primary endpoint. We have already discussed the heart failure. So moving on to stroke, the SHEP analysis indicates a 36 percent reduction in stroke for diuretics; whereas, the ALLHAT trial indicates that the alpha blocker has a 19 percent higher rate of stroke.

If you use the Hasselblad and Kong imputed placebo approach as a way of trying to merge this information, one then draws the conclusion that there

is a 24 percent reduction in the rate of stroke from the alpha blocker versus an imputed placebo. But that confidence interval includes one. So this data would not be viewed as significant evidence of a favorable effect on stroke.

If you do the same kind of analysis on the primary endpoint of fatal CHD and non-fatal MI where SHEP indicates that diuretics have a 27 percent reduction and ALLHAT indicates that the alpha blocker is three percent worse than diuretics, one gets an estimate of about a 24 percent reduction, but a confidence interval that essentially is at one.

So bottom line, what is this saying? What it's saying to me is we have certainly clear evidence that the alpha blocker provides a beneficial effect on hypertension, on blood pressure. There is also the anticipated effects, lipid effects. However, as suggestive as these markers may be of clinical effects, there are a myriad of examples in the literature that have shown that, until one actually validates that the intervention that achieves these marker effects actually achieves the clinical effects mediated through those marker effects, there is uncertainty.

The best data that I can see from what is

available, if we are really trying to say from all of this information what does doxazosin do relative to important clinical endpoints, it's the combination of information from ALLHAT and studies such as SHEP.

The data do, to my way of thinking, clearly show that diuretics are effective in reducing the risk of heart failure by a factor of two, and suggest that the alpha blocker has no effect on heart failure.

Relative to stroke and to the primary endpoint of fatal CHD and non-fatal MI, SHEP provides significant evidence of favorable effects on both of those endpoints. ALLHAT suggests that the alpha blocker is less effective in stroke, possibly because of the blood pressure issue, and essentially the same, if not just slightly less effective, on the primary endpoint.

Clearly, then these data do not establish superiority of doxazosin to the diuretics. Do they, though, at least establish efficacy through a noninferiority argument using an imputed placebo analysis?

Even with that much weaker standard, the data do not establish significance for an effect of the alpha blocker on stroke, and are essentially

marginally adequate for establishing significance on fatal CHD and non-fatal MI. I'll argue that's using a method that many of us would argue is relatively less rigorous than the typical standard we would ask for today in designing an active controlled trial.

So using even a very permissive approach, these data don't establish that there is, in fact, an effect. They are suggestive of an effect on stroke. They are suggestive of an effect on fatal CHD and non-fatal MI. But they don't prove an effect according to the standards that we would rigorously ask for today if we were designing a noninferiority trial design.

So in essence, to summarize, far and away, even with issues of concern with ALLHAT, ALLHAT provides far and away the most informative source of information about the effect of doxazosin on the critically important clinical endpoints of fatal CHD, non-fatal MI, and stroke and heart failure; and evidence suggests no effect on heart failure. Evidence suggests favorable effects on stroke and fatal CHD, non-fatal MI. But not at a level of rigors that we would typically require from a noninferiority trial design.

ACTING CHAIRMAN BORER: Tom, can I ask for a clarification here? You looked carefully at the

SHEP data, the available data, and that's a large trial.

My perception is that when we've used the putative placebo concept to determine efficacy with an active comparator, we've typically looked across multiple trials to make sure that the difference between placebo and active drug is relatively consistent, so that we can be reasonably certain that the placebo effect we are imputing or the difference from placebo we are imputing is probably right. But here we are using one trial.

Is it big enough so you can be reasonably confident of that approach?

DR. FLEMING: Well, in the interest of brevity, I didn't get into any of those very key questions that you've just raised. The typical analysis that we would require for a noninferiority comparison, as you say, Jeff, requires substantial precision in estimating the effect of the active comparator and the ability to say with confidence that the effect of the active comparator, in this case the diuretic whose effect is understood through SHEP, that that effect as estimated in SHEP is relevant to, specifically in this case, effects in ALLHAT.

It's the reason I said the analysis that

I had given that doesn't meet the standards for strength of evidence is, in fact, a permissive or lenient analysis, because it hasn't begun to address the relevant points that you have made.

I have only used SHEP. It's a single study, and it's certainly questionable as to whether the estimates of the diuretics effect in SHEP apply to exactly to what the diuretics would have yielded in ALLHAT.

ACTING CHAIRMAN BORER: Bob?

DR. TEMPLE: You would be hard put to make the case for a noninferiority design probably in any antihypertensive study, but certainly here; because the populations are always different from one to the other.

This isn't the SHEP population. It isn't even that much like the SHEP population. How can you in this study decide what the effect size is actually going to be? You have to make some major assumptions like it's going to be the same as in SHEP, which may be, maybe not. These people are all getting their lipid -- Well, some of these people are getting their lipids aggressively treated.

It's very different. I don't read them as having tried to do a noninferiority design or tried to

address the question do any antihypertensive drugs work, which is what we usually do in noninferiority studies.

They make the assumption, probably -- I mean, we could ask -- that if you lower blood pressure, it probably does things in a good direction. The question is whether lowering it with one thing is better than lowering it with another.

That, of course, you can ask and get an answer: I couldn't show it or I could. But the usual noninferiority paradigm where you are using it to try to see if the drug has any effect at all -- there was no preparation for that in this case. That's not what the trial was for.

DR. FLEMING: Absolutely. I agree fully, Bob. The analysis as I have presented essentially is anticipating discussion which says -- and in fact, the sponsor presented this -- the primary endpoint result looks the same. The primary endpoint result on non-fatal MIs and cardiovascular deaths were the same between diuretics and alpha blockers. Hence, isn't that a positive result?

If one wished to take that approach, then rigorously, in essence, what one has to ask is whether the evidence of the same effect is sufficiently

compelling that allows us to reliably conclude that you're better than a placebo.

I'm not arguing that is adequate. I'm arguing, even if you take that permissive approach here, you still don't even satisfy a permissive application of a noninferiority argument.

If we then, however, move to a higher standard, which is to say we actually have to show superiority which, I would argue, could be reasonably defended for many reasons -- one of those is the set of reasons you've just mentioned -- how do you come up with a permissible margin in this case to justify noninferiority?

Another is to say, if you are comparing to an active comparator that is accepted to be better on another and very important element, i.e., heart failure, then don't you need to show superiority? That is in essence what I think the study team has decided is the minimum standard. It is, in fact, the reason they justified termination.

You can only justify termination, in my view, of the ALLHAT trial regimen of alpha blockers if you conclude that the minimum you have to achieve is superiority, because the conditional analysis that they gave was stating, given what you currently have,

even if you have the beneficial effect we hope to have, you only have a one percent chance of achieving superiority; hence, we're stopping.

Well, the logic of that says it's not acceptable to achieve anything less thana superiority argument. I accept that argument. I'm saying, if one, though, is even far more permissive and takes the approach here of saying, well, maybe this is a positive study since results overlap, anticipating that discussion, I wanted to at least put things in the context of noninferiority, which would be the basis for justifying that conclusion.

DR. TEMPLE: But, Tom, is that what they really did? When someone asked Jeff specifically, what he said was there was no chance of showing an overall advantage. But in addition, we found this clear disadvantage on something that was important.

So I don't know how that fits into the usual noninferiority trial. It's not exactly the same.

DR. FLEMING: You and I are saying the same thing. That's what I just said. That's what they are doing. That's what, in fact, I consider to be relevant as well. However, if one is much more permissive than that, saying you don't have to show

superiority, SHEP has proven diuretics are very effective on the primary endpoint, yielding a 27 percent reduction in the rate of the primary endpoint. Isn't it enough to show it's the same?

We were shown those data. The sponsor made that point. So if you are going to make that argument, my point is even that argument doesn't statistically rigorously hold, because then you have to argue in terms of noninferiority, and for all the reasons you've said together with the statistical analysis I've given, it doesn't meet the criteria we would have even for noninferiority.

ACTING CHAIRMAN BORER: Tom and then Steven and Ralph.

DR. GRABOYS: Well, I'll take a 30 second editorial comment, because I don't really understand all the incredibly complicated statistical analysis. All I know is that as a clinician and going back into the community, because that's really the bottom line, is what we are trying to do is do the right thing for our patients in the community, is that I see a red flag here, that there is something awry and that we haven't reached closure on that, and I don't expect us to reach closure.

We are talking about a drug that is being

used increasingly in an elderly population who are developing BPH. We are using a drug in individuals who need to be treated for their hypertension, but what I am hearing and seeing is that in the community it's not uncommon for us to see 75, 80, 85-year-olds who are coming in who will need a drug for their BPH and need a drug for their hypertension, and these folks, I think, can best be served by acknowledging that there is a red flag, that there's something wrong perhaps with the drug in this population.

If that's the case, we have to take a step back and seriously consider how we are labeling this drug.

ACTING CHAIRMAN BORER: Steve?

DR. NISSEN: Tom, I'm concerned about some of the confounders here in comparing SHEP with ALLHAT. One of them I'm very concerned about is the lipid issue.

We have seen in some other trials -- the one I remember the best was the QUIET study -- where patients with very high LDL levels, the amount of benefit they got from the ACE inhibitor was very different from those that had low LDL levels.

So since we have no information here about lipid lowering therapy, I am very worried that this is

a really important confounder that we just can't analyze with what's in front of us.

The second confounder that I'm terribly worried about is dose and dose titration, that again, you know, if it's true that the dose that was ultimately used in this ALLHAT study was an inadequate dose, then it doesn't make as much sense to look at this in comparison to a trial where presumably adequate doses of the drugs were being used.

Would you comment on those two confounders and your thoughts about them?

DR. FLEMING: The first point is well taken. It is related to Bob's concern that an noninferiority analysis that takes the estimate of the effect of diuretics from SHEP and imputes that in ALLHAT is risky, and we are all on the same page.

I'm arguing, even if you make the assumption that it's sufficiently reliable to do a noninferiority analysis, you still don't meet the standard for strength of evidence that you would require.

So your points, Bob's points -- and I agree with them -- strongly urge us to be very cautious about any noninferiority assessment. The consequence of that, though, is that simply showing

the same result, a point estimate of the same result on the primary endpoint, isn't rigorously adequate evidence of a establishing benefit.

One is left, in essence, in those types of settings with needing to establish superiority and, in fact, that's the way the protocol was interpreted, the results were interpreted, when this study was terminated.

ACTING CHAIRMAN BORER: Ralph and then Ray.

DR. D'AGOSTINO: Tom, let me ask a different view of this, or ask about a different view of this study.

When we sit on these data safety monitoring committees, we oftentimes do the computation of will we show a positive effect, possibly show a positive effect on effectiveness, and we oftentimes lay that out. But I must admit that we, at least the committees I'm on, do that, and we realize that maybe the data is not all there and so forth, and we sort of look at it. But what oftentimes drives these committees is safety concerns.

I'm not sure that the stopping of the study or the stopping of that arm was driven by safety. They don't care about this noninferiority or

superiority, if they've flagged a safety issue.

Then in many of these data safety monitoring committees you jump all over the place in terms of looking at that outcome. With the cardiovascular, unfortunately, cardiovascular studies where the normally safety outcomes now become efficacy outcomes and is a real confusion.

So if you were to step aside and say let me forget for a moment the noninferiority and superiority, but do I have a really big flag for safety and should I respond to that, how do you --

DR. FLEMING: Ralph, I agree that issues of safety are certainly going to be weighed heavily, and in this setting -- this might be semantics here -- do we view the more favorable effects on heart failure by the diuretics arm to be an efficacy issue or a safety issue as it reflects the alpha blocker?

That, to my way of thinking, is somewhat semantics, because in fact a favorable benefit on heart failure is efficacy, and that may be the cause of the difference. It may, in fact, reflect a favorable effect by diuretics or an unfavorable effect may, in fact, reflect harm that's induced by the alpha blocker.

Actually, if I am on the data monitoring

board, in a certain sense the semantics, to me, don't matter. The reality is heart failure is a very important clinical endpoint itself, an important secondary measure, and I have two interventions in hand here. One of those interventions, diuretics, is clearly better than the other, alpha blockers.

As a result, it is an additional basis that justifies my conclusion then that, unless alpha blockers are better on the primary endpoint, then I don't have a favorable benefit to risk profile, not even mentioning other things such as cost.

DR. D'AGOSTINO: What I'm obviously raising is that the study, the ALLHAT study, in and of itself, one could ask these questions: I have this dataset in front of us; how do I respond to it?

I think, as you are describing now is the way to start piecing it together. But I think it's a different -- It's a different set of concerns and different set of considerations than this noninferiority type of aspect: Am I so upset by what I see?

ACTING CHAIRMAN BORER: I think before Ray makes his comment, I want to remind everybody of the gist of an earlier portion of this discussion. That is the potential importance -- we may not be able to

resolve it, but the potential importance of separating harmful effects for the myocardium that may affect natural course, etcetera, etcetera, and the development of pulmonary vascular congestion without intrinsic damage to the myocardium; because if you knew that such a difference existed, you might choose a different strategy to deal with patients who manifested the symptoms.

Again, I'm not taking a position on this, because we don't have the data. But we do have to consider that in our thinking. Ray, you made that point, and you had a comment here.

DR. LIPICKY: Well, I was going to suggest that you might start answering the questions, because all these are really responding to an overview which was erudite but could be picked on for the next hour and a half.

ACTING CHAIRMAN BORER: Okay, very good thought. In fact, it was the very suggestion I was about to make. So with that superb suggestion --

DR. KONSTAM: Hey, Jeff, could I just ask Tom one question, because maybe I'm looking at this a little differently. One thing that I want you to address, I'm not sure whether you've addressed or not.

You know, we wouldn't be sitting here

today if there were not some differences in terms of nominal p-values, in terms of some endpoints between chlorthalidone and doxazosin. So the question I have is: What do you do with those p-values for secondary endpoints, and particularly components of secondary endpoints, when you have no significant difference in your primary endpoint?

DR. LIPICKY: That's a specific question that you will have to address. It's on the list.

DR. KONSTAM: Okay.

ACTING CHAIRMAN BORER: Okay. We'll begin then with the questions. What I want to do here is to allow everyone to make a short response to each of these questions, because this is a very difficult set of issues to resolve, and I think, for the FDA to get optimal advice, it should hear the varied opinions of all the people that it has empaneled.

Some of these questions depend more on clinical judgment than on statistical judgment, some more on statistical analysis than clinical judgment, and we will try to vary the order of response, depending upon my judgment of which of these this is.

The first one, the first question is: Consider the following issues related to the interpretation of the ALLHAT findings regarding

doxazosin. 1.1, I think, really does require a little bit of clinical judgment here. That is:

1.1 The ALLHAT protocol restricted the maximum dose of doxazosin to 8 mg, but the label encourages use up to 16 mg. ALLHAT had dose titration at one-month intervals, but the label encourages titration at one to two-week intervals. Do the results of ALLHAT apply to doxazosin when it is used as labeled?

Why don't we begin at one end, on Marvin's end, and move this way. Marvin, you made some cogent comments about this. Why don't you start out? I'm sorry. Bob?

DR. FENICHEL: I guess there are two different ways that the question could be interpreted, though. One is do the results apply to doxazosin as it is used, period, meaning how do the ALLHAT results apply -- how do we think they apply to the population now receiving doxazosin presumably on the basis of its label.

Then a different question is how do the ALLHAT apply to a hypothetical population whose physicians were actually conforming to the behavior suggested in the label? That's a different population. That's a different and hypothetical

population, but that's important.

Well, it's important. Let me just clarify it in a very quick way. What we heard, I think, from several sources is that people, in fact, don't use 16 milligrams. The labeling says they ought to on occasion, but in fact they don't.

So the first question is how does the ALLHAT physician behavior compare to the real behavior out in the world. The second question is how does it compare to the proposed behavior which is now in the label?

DR. LIPICKY: So maybe some clarification has to be made in the questions. I understand the distinction being made. We don't know how doxazosin is used in practice or for whom it's used in practice. That data hasn't been presented. So I don't see how we can answer that question.

DR. FENICHEL: Well, people alluded to it.

DR. LIPICKY: I don't see the data. Do you have it written down somewhere? Okay, so we don't have it.

ACTING CHAIRMAN BORER: What I will try to do, since Marvin actually raised that issue himself in his earlier comments, we'll try to deal with --

DR. LIPICKY: Well, I suggest you don't

deal with that. You don't know what you're dealing with.

ACTING CHAIRMAN BORER: Okay.

DR. LIPICKY: We had written a label for doxazosin that says use doxazosin thusly. That is the label that we have to make a modification to, and to just make the illustration complete, if I had to incorporate ALLHAT results in the labeling, what I would say is don't use doxazosin like it was used in ALLHAT. I wouldn't be able to say don't use doxazosin because look at what ALLHAT found.

Okay. So it is to the existing labeling, and we can deal with that. We know what the existing labeling is, and the other business we can swim around in for a long time.

ACTING CHAIRMAN BORER: Okay. Marvin, why don't you begin?

DR. KONSTAM: I was just going to say no as my answer to the question. Now I don't know what to say. I mean, the question as asked, I think the answer clearly is no. I mean, ALLHAT did not deploy the drug as used in the label, and from what we hear -- So we don't know how it's used in practice.

The information that I'm hearing about how it's used in practice -- I think the answer would also

be no, because I heard in the majority of cases it's not used as first line therapy. So I think the answer is going to wind up being no for both.

ACTING CHAIRMAN BORER: Bob, did you want to make a comment?

DR. TEMPLE: Well, I just think -- I think Bob Fenichel's question is of interest and ought to be addressed. I mean, if in fact -- and I know Pfizer can tell us or others can tell us -- almost nobody is using 16 milligrams and everybody sort of does a leisurely titration, it may be highly relevant to the way it's used, especially if we don't know why they are not using the right dose.

Maybe there's a reason. We don't know that. So I would like to hear people comment on both of those things.

ACTING CHAIRMAN BORER: Okay. We can certainly do that. The fact is that we are going to get to an answer to that question further down the list, even though it's not specifically stated. So we are going to have to deal with it one way or the other.

Be that as it may, let's go on to Michael.

DR. ARTMAN: No, I don't think you can extrapolate to a higher dose and a more rapid

titration. So I don't think it is applicable.

ACTING CHAIRMAN BORER: Ileana?

DR. PINA: No.

DR. HIRSCH: No, but it's not the relevant question.

ACTING CHAIRMAN BORER: Do you want to make a comment about the relevant question?

DR. HIRSCH: Sure. The relevant question is: ALLHAT was designed by its investigators, and the petitioners' design asked us how it's applied in the real world. So I think we really have to come back and ask that question. Compared to the real world, does this provide us guidance? But we'll get to that in a minute.

ACTING CHAIRMAN BORER: Okay. Tom?

DR. GRABOYS: Yes. The real world is all anecdotal at this point, but I think it's substantiated by the folks from Pfizer who indicated that it -- you don't go up, and rarely do we see these folks going up to 16. It's much lower than that. So I guess I'm along the "no" line.

ACTING CHAIRMAN BORER: Joan, you don't vote. Tom?

DR. FLEMING: I don't know the answer to this, partly -- well, for two reasons. First of all,

I don't know whether, if you had a two-weekly rather than a monthly titration with a maximum of 16 rather than 8, whether that matters in terms of efficacy. I don't know.

I also don't know how important it is because if, in fact, the way the clinical practice proceeds is largely consistent with ALLHAT, then this is not a relevant issue. If it is very different, if people would, in fact, use more rapid titration and go to 16 frequently, then the question is more relevant. But still, I don't know whether that would have impacted safety and efficacy.

DR. LIPICKY: But can I interject with Tom. You do know that the greater the dose, the greater the blood pressure reduction up through 16. And you know that in the study the blood pressure reduction was less than with the other drugs, and you know that the treatment of hypertension is supposed to influence the variables that were measured.

So what is it that's missing from your logic?

DR. FLEMING: True, true and true.

DR. LIPICKY: Yes? They are unrelated?

DR. FLEMING: What's missing is that I'm going to have to now make the assumption that, if you

had the titration schedule on two-weekly rather than monthly, allowing --

DR. LIPICKY: No, no. Forget the titration. Just dose.

DR. FLEMING: -- allowing to go to 16 rather than 8 -- if you had that, your question requires me to somehow model whether or not that would have eliminated the difference in systolic blood pressures. There were no differences in diastolic.

So assumption one, model one is, if I did take the different maximal dose, the question is: Would that have altered the overall blood pressure control to a level that would have given me comparable control with the diuretic?

I don't know the answer to that. It might have. That's point one. That's assumption one.

Assumption number two is: Even if it had, would that have made a difference in the endpoint? Well, you're asking the wrong person, if you want somebody to believe in surrogates.

DR. LIPICKY: That's correct, but let me put it this way. Let's say I -- Let's just make the thing more exaggerated. Let's say that doxazosin was placebo. So it was the equivalent of a very small dose, but let's say it was .001 milligrams of

doxazosin, but people were randomized to doxazosin.

Would you now be willing to conclude -- and the results were the same. Let's just make that assumption, and you did an intent-to-treat analysis. Would you now conclude that doxazosin caused the heart failure, because that's what you are doing here in your unwillingness to accept the notion that you ought to study things that at least they are the doses that the instructions for use include.

DR. FLEMING: I'm not arguing that they shouldn't have used 16. I don't know what the right answer is. I'm just responding to your assumptions that you have made, pointing out that those are assumptions that may be true, but they may not be true.

DR. LIPICKY; Well, I guess I'm not making the assumptions that the question asks: Are the results applicable to the current labeling?

DR. FLEMING: The results are clearly applicable to what was defined as the regimen in the protocol.

DR. LIPICKY: Yes.

DR. FLEMING: Now whether they are applicable to the label requires insight that I don't have, and that is, if you had in fact instead had the

protocol have 16, (a) would that have yielded a different blood pressure control, and then another major assumption (b) would that have translated into a better control of stroke and a better effect on heart failure?

I don't know the answers to those. My second original comment was I don't even know how important the question is, because if, in fact,the actual implementation of the protocol specified regiment doesn't meaningfully differ in the vast majority of cases from the actual implementation of the label, then it isn't a critical issue, and I don't know whether that's true.

ACTING CHAIRMAN BORER: Joann?

DR. LINDENFELD: I have to agree. I don't think that the current results of ALLHAT apply when doxazosin is used as labeled, but again I can't really answer this because we don't know exactly how it's used. That's a different question.

ACTING CHAIRMAN BORER: Steve?

DR. NISSEN: Yes. I agree with everyone else, but I would add one more point. We don't really even know how doxazosin was used in ALLHAT. I mean, i don't know what the mean dose was.

So there is absolutely no way to answer

this without having the data. So, you know, we know what the maximum possible dose was, and that's all we know. I think you can't extrapolate that to the label without knowing more. So we really have a vacuum there.

ACTING CHAIRMAN BORER: Bob?

DR. FENICHEL: No.

ACTING CHAIRMAN BORER: Ralph?

DR. D'AGOSTINO: No.

ACTING CHAIRMAN BORER: Okay. And final vote, I agree. I think that we can't say that it applies to the label or to doxazosin when it's used as labeled, because we don't have the data, and we don't know what was done, just as Steve said.

That sounds like a fairly unanimous response, Ray, for your advice.

DR. LIPICKY: Thank you.

ACTING CHAIRMAN BORER: You're welcome.

At three years, only 76 percent of subjects randomized to doxazosin were still taking it. How should subjects not taking doxazosin be included in any analysis?

This seems to have more statistical than clinical implications. Why don't we begin with Ralph and then Tom, and we'll see if anybody disagrees with

what they say.

DR. D'AGOSTINO: I think the appropriate analysis is an intention-to-treat analysis. I do think, though, that as you do these analyses, you want to have a sense of what happens in subsets. What happens if I perturbate the data? Do I still see a robust result?

In that context, the ALLHAT investigators looked at, I think, gender differences or gender groups and looked at age groups and saw a robustness. I think that in order to really feel comfortable interpreting the results, I would like to see this type of an analysis where those who took the drug, in fact, are analyzed. I don't expect a different result.

I mean, when we do these things, they tend to give the same -- but for completeness. There's also the question, which is not here, that if I again read the article correctly, they only had data on 92 percent or so of the individuals. I'd like to see what would happen if you took as many individuals as possible in your analysis.

It's more for the robustness of it, not that I think that you would end up getting a different result, and it's sort of the general question of

completeness of the analyses which is touched on in a number of these questions, and the availability of the data that this alludes to. In that case, I think that this plus other analyses really do need to be performed before we can feel really comfortable with the ALLHAT results.

ACTING CHAIRMAN BORER: Tom, what should we do with the other subjects?

DR. FLEMING: I think I largely agree with what Ralph has already said. The protocol is designed to answer a question, which I think is a very relevant question. That is, what strategy is to be preferred when you look at overall benefit to risk, a strategy that is based on the diuretic or a strategy that's based on the alpha blocker?

Certainly, in any trial you are going to have people who are not adherent, people who can't tolerate the therapy, people who may take other supportive care. The overall intention-to-treat analysis is the analysis that gives us the unbiased and, I think, most interpretable results.

The 24-5 percent of people who had three years weren't on doxazosin, are people who are intrinsically different than those who were, and I have to in essence, if I'm going to exclude them,